*Critical Reviews in Toxicology,* 33(6):581–589, 2003

ISSN: 1040-8371
DOI: 10.1080/10408440390250073

## Invited Review

# The Human Relevance of Information on Carcinogenic Modes of Action: Overview‡

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**ABSTRACT:** Risk assessment policies and practice place increasing reliance on mode of action (MOA) data to inform conclusions about the human relevance of animal tumors. In June 2001, the Risk Science Institute of the International Life Sciences Institute formed a workgroup to study this issue. The workgroup divided into two subgroups, one developing and testing a "framework" for MOA relevance analysis and the other conducting an in-depth analysis of peroxisome proliferation-activated receptor (PPAR)$\alpha$ activation as the MOA for some animal carcinogens. This special issue of *Critical Reviews in Toxicology* presents the scientific reports emerging from this activity. These reports serve several purposes. For risk assessors in and out of government, they offer a new human relevance framework (HRF) that complements and extends existing guidance from other organizations. Regarding the specific MOA for peroxisome proliferating chemicals, these reports offer a state-of-the-science review of this important MOA and its role in tumorigenesis in three different tissues (liver, testis, and pancreas). The case studies in these reports present models for using MOA information to evaluate the hazard potential for humans. The cases also illustrate the substantial impact of a complete human relevance analysis, as distinct from an animal MOA analysis alone, on the nature and scope of risk assessment.

**KEYWORDS:** carcinogenic mode of action, human relevance of animal tumors, peroxisome proliferation, PPAR$\alpha$ agonists, risk assessment.

Received June 13, 2003; accepted July 27, 2003.

‡Although guidance proposed by the U.S. EPA and IPCS (U.S. EPA, 1999; Sonich-Mullin et al., 2001) served as a springboard for some aspects of this project, the work reported here was conducted independently of the ongoing efforts of both organizations. This ILSI Risk Science Institute project was supported by funding from several offices of the U.S. Environmental Protection Agency and the Existing Substances Division of Health Canada.

The views expressed in this report are those of the individual authors and do not necessarily reflect the views of ILSI, U.S. EPA, Health Canada or any other organization. Mention of common or trade names of commercial products does not constitute endorsement or recommendation for use.

## INTRODUCTION

Two critical assumptions have governed cancer risk assessment for many years. In the absence of information to the contrary, risk assessors generally assume that tumors observed in laboratory animals are predictive of human cancer and that the mode of action (MOA) defined in laboratory animals applies also to humans (IARC, 1992; NRC, 1994; Sonich-Mullin et al., 2001; U.S. EPA, 1999; Vainio et al., 1992). In June 2001, the Risk Science Institute of the International Life Sciences Institute (ILSI RSI) formed a workgroup to examine these issues, with a focus on using MOA information to determine the human relevance of animal tumors. The workgroup divided into two subgroups, one developing and using a framework for MOA-based human relevance analysis (human relevance framework, HRF) and the other studying peroxisome proliferation activated receptor (PPAR)$\alpha$ activation as an element of the MOA for certain rodent chemical carcinogens and the human relevance of this MOA.

To develop useful new perspectives for risk assessment guidance and practice, the Framework Subgroup studied several different MOAs, each illustrated by a different animal carcinogen. The experience and insights gained are the subject of the first of two ILSI RSI reports in this issue, "A Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action" (Framework Report). The HRF emphasizes the importance of transparent, weight-of-evidence principles and methods for assessing the human relevance of MOA information from animal and human sources. The HRF is based primarily on the case studies that form the core of this article.

Starting from a different point, the PPAR$\alpha$ Agonist Subgroup focused on defining MOAs for peroxisome proliferating agents that interact with PPAR$\alpha$. This subgroup first reviewed the available scientific data as a basis for hypothesizing MOAs in animals and then examined the weight-of-evidence for their relevance to humans. The second article in this issue, "PPAR$\alpha$ Agonist-Induced Rodent Tumors: Mode(s) of Action and Human Relevance" (PPAR$\alpha$ Agonist Report), presents a state-of-the-science analysis for characterizing the MOAs, outlines steps for assessing the human relevance of PPAR$\alpha$-induced animal tumors in line with the framework, and includes several case examples.

These companion articles serve several purposes. For risk assessors in and out of government, they offer guidance and models for using MOA information, related animal tumor data, and available human information to evaluate the hazard potential for humans. The approaches developed should become mainstay tools in the scientific community's overall effort to enhance the predictive power, reliability, and transparency of cancer risk assessment.

## THE HUMAN RELEVANCE FRAMEWORK

The U.S. Environmental Protection Agency (EPA) and the International Program for Chemical Safety (IPCS) have proposed generally comparable guidance for using animal MOA information to assess the relevance of animal tumors for human risk assessment (Sonich-Mullin et al., 2001; U.S. EPA, 1999). Both proposals focus on describing measurable effects, called "key events," that are critical to tumor formation as hypothesized in the MOA postulated for laboratory animals.

The human relevance framework expands the U.S. EPA and IPCS frameworks into a new four-part analysis for use mainly in the hazard identification phase of the risk assessment process. Drawing on MOA information from both animal and human sources, the HRF calls for a weight-of-evidence analysis to inform characterization of the available tumor data as to potential human relevance. This characterization should be fully transparent as to chemical-specific and generic data sources, data gaps, assumptions about the applicability of generic data, and extrapolations within the MOA analysis.

Although the U.S. EPA and IPCS proposals provide the starting point for the human relevance analysis and are integral to this analysis, the innovations distinguishing the new HRF from its precursors are products of case study analysis. The Framework Subgroup began by analyzing several chemical examples in line with the U.S. EPA and IPCS proposals. When the subgroup discovered that the analytical framework set forth in these proposals pointed toward but did not systematically address the human relevance question, the subgroup sought other information to develop a reasonable level of confidence regarding the likelihood that animal MOA data were informative about expected effects in humans.

Expanding the focus beyond the animal MOA to human relevance led to the four-part HRF, which features two new questions and a closing analysis that distinguish this analytical format from its antecedents.

**QUESTION 1**: Is the weight of evidence sufficient to establish the MOA in animals?

**QUESTION 2**: Are key events in the animal MOA plausible in humans?

**QUESTION 3**: Taking into account kinetic and dynamic factors, is the animal MOA plausible in humans?

**CONCLUSION**: Statement of confidence; analysis; implications.

The case-study analyses varied in scope and outcome. Analyzing for several cases the animal MOA for human relevance involved data relating to each of the three framework questions while in other cases addressing the first or second question completed the analysis. For example, although considerable MOA data were available in one case (case example: acrylonitrile), further analysis made it clear that the available data were inadequate for characterizing the MOA in animals. In this case, consistent with long-standing risk assessment principles, it is appropriate to assume that the animal tumors are relevant to humans and to conduct a full risk assessment.

In contrast, modes of action involving cytotoxicity and cellular regeneration (case example: chloroform) or tissue response to bladder calculi (case example: melamine) required a complete human relevance analysis because the postulated animal MOA was qualitatively and quantitatively plausible in humans. The potential human relevance of these MOAs and related tumors necessitates a full risk assessment. It is notable, however, that even though the melamine MOA meets qualitative and quantitative tests for human relevance, preliminary exposure considerations suggest that human exposure to this particular chemical is low to nonexistent, with the result that the chemical would not pose a risk to humans.

Several cases represent intermediate situations in which the postulated animal MOA finds support in the database but is not relevant for human risk assessment because human counterparts are unlikely. For example, when the "Question 2" analysis identifies species-specific factors such as a tumor-related protein (case example: *d*-limonene) not found in humans or hormonal changes in laboratory animals with no human counterpart (case example: atrazine), the animal MOA is judged not relevant to humans. Similarly, when the animal MOA was plausible in humans because of comparable key events, but further analysis of quantitative variables disclosed substantial differences in hormone clearance rates (case example: phenobarbital), the animal MOA is unlikely to operate in humans and the related animal tumors would not be relevant for human risk assessment.

The general schematic in Figure 1 illustrates the relation between human relevance and risk assessment. Each conclusion is specific to the MOA and tissue or cell type and endpoint under study.

The HRF adopts the customary presumption that animal tumors are relevant for human hazard or risk assessment. Similarly, the animal MOA is presumed to describe processes in humans as well as in animals. Although the presumption of relevance applies alike to DNA-reactive and non-DNA-reactive carcinogens, presumptive judgments of human relevance for non-DNA-reactive carcinogens often generate greater controversy and stimulate calls for MOA data to rebut the presumption as to individual chemicals. To augment guidance currently available on this contentious issue, this special issue focuses mainly on non-DNA-reactive carcinogens, with special attention to the human relevance of the MOAs associated with PPAR$\alpha$ agonists.

## PPAR$\alpha$ AGONIST-INDUCED RODENT TUMORS

For many years, the scientific community has been interested in using MOA information to understand and explain the significance to humans of animal tumors induced by "peroxisome proliferating" chemicals. In December 1995, the International Life Sciences Institute's Health and Environmental Sciences Institute held a workshop to review the state of the science on the relationship between peroxisome proliferation and hepatocarcinogenesis and to seek consensus on the meaning of these data for human hazard and risk (Cattley et al., 1998). Conclusions reached at the workshop included agreement on the kind of information needed to characterize a chemical as a peroxisome proliferator, that is, a chemical whose carcinogenic MOA depends in some way on this phenomenon. Participants also agreed on the kind of data needed to support a margin of exposure (i.e., nonlinear) risk assessment approach for these chemicals.

Important new information on the mechanism(s) by which peroxisome proliferators produce certain carcinogenic responses in rats and mice, including advances in understanding the underlying genetic factors that mediate biochemical and cellular responses to such chemicals, has emerged since the 1995 workshop. This article summarizes the

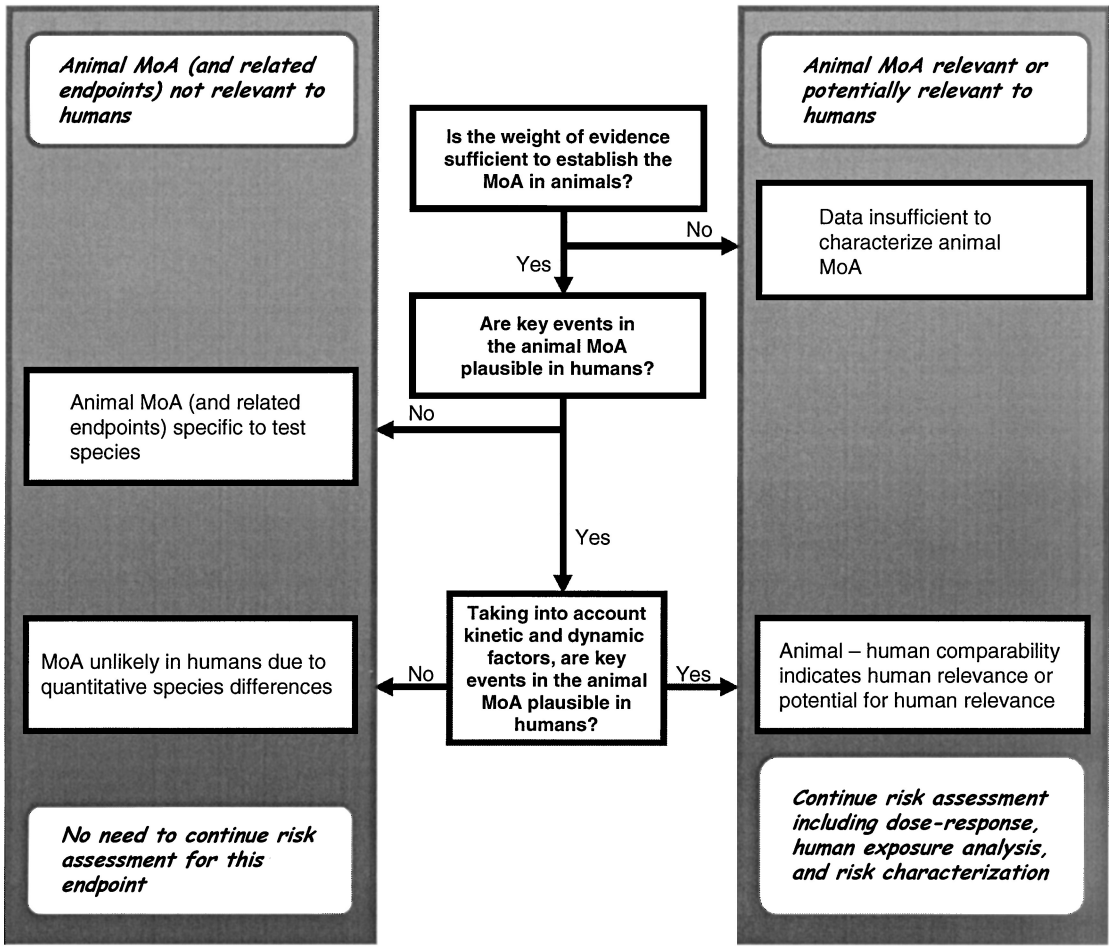


**FIGURE 1.** General schematic illustrating divergent outcomes for different MOAs analyzed in line with the four-part human relevance framework. The left side depicts data-based findings that animal tumors are unlikely to be relevant for human risk assessment because a tumor-related animal MOA is unlikely to have a human counterpart for the endpoint under study. The right side portrays outcomes leading to complete risk assessments based on comparable animal and human MOA information indicating the likely human relevance of animal tumors.

work of an International Life Sciences Institute Risk Science Institute Workgroup charged with updating the 1998 report of the 1995 workshop and describes workgroup conclusions regarding the human relevance of PPAR$\alpha$ agonist-induced tumors observed in rodent liver, pancreas, and testis (Leydig cells). This article summarizes work in which new MOA information on a subclass of peroxisome proliferators was evaluated in line with the new approaches to evaluating the human relevance of animal tumors.

Peroxisomes are subcellular organelles found in the cytoplasm of mammalian cells. They have important metabolic functions. Peroxisomes are known to proliferate under a variety of altered physiological and metabolic states, most notably with the availability of high concentrations of unsaturated and polyunsaturated fatty acids. While these physiologic adaptive responses have been known for some time, greater interest in peroxisome proliferation was generated when extensive peroxisome induction was noted in rodent hepatocytes and hepatic tumors developed in intact rodents in response to the administration of certain xenobiotics (Hess et al., 1965; Reddy et al., 1976). Based on the observation of peroxisome proliferation, the wide array of chemical and pharmaceutical agents that induce this response have been collectively referred to as "peroxisome proliferators." Examples include hypolipidemic drugs in the fibrate class such as clofibrate and gemfibrozil, phthalate ester plasticizers such as di(2-ethylhexyl) pthalate (DEHP), di(2-ethylhexyl) adipate (DEHA), and diisononyl phthalate (DINP),

pesticides such as diclofop-methyl and lactofen, and chlorinated solvents such as trichloroethylene and perchloroethylene.

Several PPAR$\alpha$ agonists have demonstrated carcinogenicity in mice but not rats. The reverse is true for clofibrate but otherwise has seldom been observed; admittedly, not all of the PPAR$\alpha$ agonists have been tested fully in both species. In some cases, the metabolism of the substance in rats and mice is different, leading to inactive or low levels of active metabolites in rats compared with mice (Ashby et al., 1994). In addition, it appears that a minimum level of increased peroxisomal enzyme activity is necessary in order to elicit a statistically significant increase in tumor incidence (Ashby et al., 1994). Increases in palmityl coenzyme A (CoA) enzyme activity levels for various plasticizers are consistent with an apparent threshold for tumor induction. However, due to limitations in the sensitivity of carcinogenicity bioassays in general, the existence of a threshold is difficult to demonstrate empirically.

As noted earlier, some PPAR$\alpha$ agonists also induced tumors in rats and/or mice at sites other than the liver. For example, steroids such as testosterone and growth factors such as cholecystokinen (CCK) stimulate neoplastic growth in pancreatic acinar cells in rats (e.g., Longnecker, 1987). In related mechanism studies, these and similar compounds appear to exert their effects by increasing bile acid synthesis, altering bile acid metabolism or both during cholestasis. However, the weight of evidence is weak compared to the liver.

A number of PPAR$\alpha$ agonists have been reported to induce testicular (Leydig cell) tumors in rats. These include clofibrate, DEHP, DINP, gemfibrozil, methylclofenapate, perchloroethylene, perfluorooctanoic acid, and trichloroethylene (Biegel et al., 2001). Interestingly, Leydig-cell tumors were observed only when these compounds were tested in non-F344 male rats. It is known that by 2 years of age, the F344 rat has virtually a 100% incidence of spontaneously occurring Leydig-cell tumors, which would make it difficult, if not impossible, to detect a xenobiotic-induced testicular tumor in this strain. The finding that a relationship appears to exist between PPAR$\alpha$ agonists and Leydig-cell tumor formation has led to the speculation that many, if not all, peroxisome proliferators could produce this tumor if tested adequately in a rat strain other than F344.

After attempting to characterize the animal MOAs for PPAR$\alpha$ agonists in the three tumor types, the subgroup undertook human relevance analyses for several chemicals in line with the new HRF. Because this analysis varies in accord with the availability of MOA information from human studies as well as laboratory animal data, the subgroup chose chemicals that varied in terms of the amount and quality of data relating to the MOA for PPAR$\alpha$ agonist-related rodent liver tumors. For example, DEHP is a model for chemicals with a robust animal database but minimal human data of the kind required for human relevance analysis. Although limited, the available data from humans and nonhuman primates permit a conclusion that the animal MOA for this tumor is unlikely in humans through the PPAR$\alpha$ agonist MOA (Table 1). In this case, as already illustrated in Figure 1, further assessment based on this tumor type would not be required. Because DEHP produces other tumors as well, additional analyses would be required before determining what additional risk assessment would be needed.

The MOA and human relevance analyses produce the same result for another liver carcinogen, clofibrate, which has considerable human data but a less robust animal database In this example, the differences between key events and related processes in animals and humans suggest that the carcinogenic events observed in laboratory animals are unlikely to occur in humans exposed to clofibrate, and risk assessment would not be required based on that tumor analysis. The results are different for another liver carcinogen, oxadiazon. In this case, although the animal database is substantial, because the available data suggest but do not support the PPAR$\alpha$ agonist hypothesis, uncertainty about the MOA for this endpoint in animals precludes the completion of a human relevance analysis. As a result, the presumption of relevance applies and a full risk assessment would be expected. In addition to these cases evaluating the human relevance of liver carcinogens, the PFOA example presents a human relevance analysis for a chemical that produces a "tumor triad" in rats—liver, Leydig cell, and pancreatic acinar cell tumors—through the PPAR$\alpha$ MOA. Figure 2 shows the results of the human relevance analyses for all MOAs in the PPAR$\alpha$ case studies.

Although several subclasses of peroxisome proliferators are known, these deliberations have focused solely on PPAR$\alpha$ agonists. The workgroup has reexamined, in light of the new data, the minimum battery of tests needed to show that the MOA for hepatocarcinogenicity is PPAR$\alpha$ driven, along with an analysis of the data available to describe the modes of action by which Leydig cell and pancreatic acinar cell tumors are produced in rats by PPAR$\alpha$ agonists that also produce liver tumors.

**TABLE 1**
**Key Events Comparison Table—Liver Tumors**

| Rat/mouse MOA key events for liver tumors | Is this key event in the animal MOA plausible in humans? | Taking into account kinetic and dynamic factors, is this key event in the animal MOA plausible in humans? |
|---|---|---|
| 1. Activation of PPAR$\alpha$ | Yes | Yes |
| 2a. Expression of peroxisomal genes | Not likely | Not likely |
| 2b. PPAR$\alpha$-mediated expression of cell cycle, growth and apoptosis | Unknown | Unknown |
| 2c. Nonperoxisome lipid gene expression | Yes—this is the molecular basis of human therapeutic response to hypolipidaemic drugs | Yes |
| 3a. Peroxisome proliferation | Not likely | Not likely—no or weak response in human biopsy material and in nonhuman primates |
| 3bi. Perturbation of cell proliferation | Not likely—not seen in many independent studies of human hepatocytes in vitro; not measured in humans in vivo; not seen in nonhuman primates in vivo or in vitro; not seen in hamsters | Not likely |
| 3bii. Perturbation of apoptosis | Not likely—not seen in limited studies of human hepatocytes in vitro; not measured in humans in vivo | Not likely |
| 4. Inhibition of GJIC | Not likely—no inhibition in primates in vitro or in vivo or in human hepatoctyes in vitro | Not likely |
| 5. Hepatocyte oxidative stress | Unknown | Unknown |
| 6. Kupffer cell-mediated events | Unknown | Unknown |
| 7. Selective clonal expansion | Unknown—no response seen in nonhuman primates | Unknown |
| 8. Liver tumors | Not likely | Not likely |

*Note*. To test the new HRF, the PPAR$\alpha$ Agonist Subgroup extended the key events analysis to the human relevance questions. This table summarizes the key events analysis (HRF Question 1) and the concordance analyses (HRF Questions 2 and 3) for PPAR$\alpha$ agonist activation in liver for DEHP, one of the case studies analyzed in the PPAR$\alpha$ Agonist Report, Section II.D.1.

## PARTICIPANTS

Senior scientists from many different organizations—academic institutions, private research organizations, industry, and government agencies—brought a broad range of expertise and experience to this activity. Participants included bench scientists who have conducted some of the MOA studies featured in this report, clinicians knowledgeable about human responses, and scientists responsible for using MOA and human relevance information for risk assessment and environmental decision-making in both the public and private sectors.

Dr. Samuel Cohen, University of Nebraska Medical Center, was the Steering Committee Chairman. Framework and PPAR$\alpha$ Agonist Subgroup members are listed next.

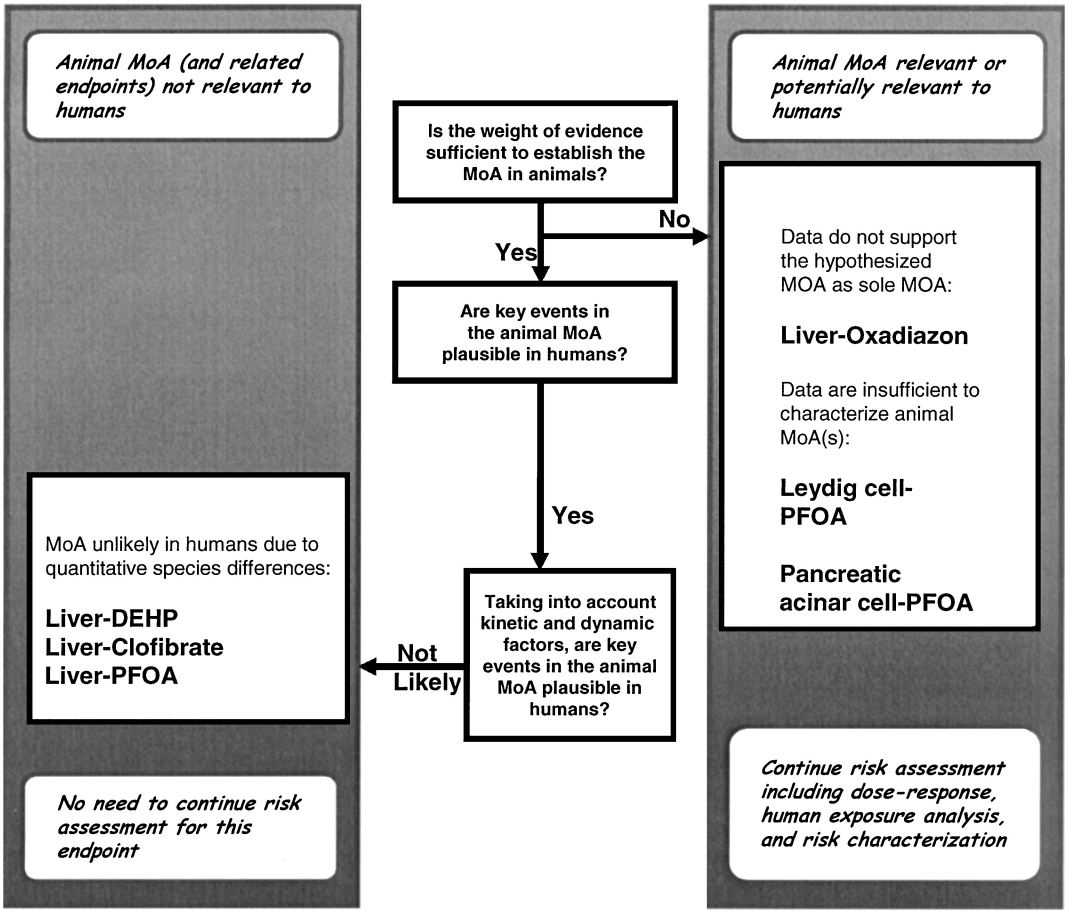


**FIGURE 2.** Summary of outcomes for all MOAs for four PPAR$\alpha$ agonist case studies, analyzed in line with the four-part human relevance framework. The left side depicts data-based findings that certain PPAR$\alpha$ agonist-induced liver tumors are irrelevant for human risk assessment because their animal MOA is not likely to have a human counterpart. The right side portrays two outcomes leading to complete risk assessments. One is the product of data-based findings showing that Oxadiazon appears not to induce liver tumors solely by the MOA hypothesized for PPAR$\alpha$ agonists. The other is the default: When data are insufficient to confidently characterize an MOA for test animals, the animal tumor data are presumed to be relevant to humans and a complete risk assessment is necessary (Leydig cell and pancreatic acinar cell-perfluorooctanoic acid, PFOA).

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## PROCESS

The workgroup adopted a highly iterative process both within each subgroup and between the two subgroups. Although participants worked mainly on a subgroup basis, the two groups regularly exchanged information, plans, and documents, with each informed by the other. In one sense, the two groups took directly opposite approaches: The Framework group began by developing case studies which then determined the nature and shape of the HRF, while the PPAR group developed a state-of-the-science report as the foundation for later selecting cases and conducting MOA and human relevance analyses.

For example, having deliberately selected chemicals with generally understood animal modes of action, the Framework Subgroup easily completed its analyses of the animal MOA (i.e., HRF Question 1) using published data and following existing U.S. EPA and IPCS guidance on this point [3, 4]. However, in developing the case studies, the group experimented with several different versions of HRF Questions 2 and 3 before settling on the phrasing and sequence outlined here. Only then was the subgroup ready to offer and explain the human relevance analysis set forth in that Report.

Taking a different approach, the PPAR$\alpha$ group devoted many months to working out the mode(s) of action for PPAR$\alpha$ agonist-related tumors in animals, with special attention to the MOA in liver, pancreatic acinar cell, and Leydig cell tumors. When the resulting state-of-the-science report neared completion, the PPAR$\alpha$ group then identified case studies for the MOA and human relevance analyses.

The ILSI Risk Science Institute invited peer review of these papers at two different stages in the development of these reports. In June 2002, ILSI RSI conducted a preliminary review of both reports, though in different modes. Six experts reviewed and provided written comments on an intermediate draft of the PPAR$\alpha$ report. For the Framework Report, ILSI RSI asked a single highly respected expert to facilitate a meeting of the Framework Subgroup to complete the case studies and the HRF. Both subgroups revised their reports in line with recommendations made at the June workshop.

In December 2002, the ILSI Risk Science Institute sponsored a 2-day workshop in Washington, DC, for peer review of the revised drafts. Reviewers included experts from many different scientific disciplines and from several different countries. Reviewers were affiliated with industry, universities, and several state and federal government agencies. The 18 peer reviewers provided written comments and oral discussion on the reports as a whole as well as on individual case studies. Following the workshop, the subgroups revised their respective reports in line with the peer review comments.

Also in December 2002, the Framework Subgroup presented a preview of this report at the Annual Meeting of the Society for Risk Analysis. In March 2003, the workgroup organized a symposium at the Annual Meeting of the Society of Toxicology, with a special focus on the PPAR$\alpha$ paper.

## ACKNOWLEDGMENT

The ILSI Risk Science Institute and the Human Relevance Workgroup greatly appreciate Dr. John A. Moore's skilled facilitation as Chairman of the December, 2002 Peer Review Workshop.

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